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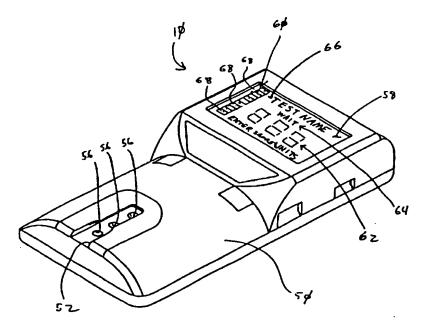
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(57) Abstract

An apparatus for the optoelectronic evaluation f test paper strips for use in the detection of certain analytes in blood or other body fluids. The test strip comprises an elongated plastic part including a hinged portion to allow a first portion to be folded over a second portion. A series of layers f test strips are disposed between the f Ided-over porti ns of the test strip. The step strip is configured such that the chemistry layers are placed in c ntacting engagement with one another, but not c mpressing one another. A reflectance ph tometer is pr vided and includes various features, including a lot number reader wherein if the test strip does not match the memory module, a test is not performed, and the user is instructed to insert a c rrect memory module.

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GA Gabon					

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# APPARATUS AND METHOD FOR DETERMINING SUBSTANCES CONTAINED IN A BODY FLUID

## BACKGROUND OF THE INVENTION

The present invention relates generally to an assay system for biological and nonbiological fluids. More particularly, the present invention relates to an apparatus for separating serum or plasma from particulate matter and then optoelectronically evaluating the serum or plasma in order to measure analytes within the serum.

It has long been desirable to utilize devices that can be used for on-site testing of blood products. Particularly important is the analysis of body fluids from humans and animals to diagnose disease, monitor the course of therapy, or determine the presence of illicit drugs. Commonly, the analytical methods used to carry out these objects are performed on blood samples.

Clinical chemists have a preference for working with serum over plasma and plasma over whole blood because of the clarity of the sample matrix and the lack of interfering substances from the solid portion of the blood. In order to facilitate analysis, a separation step must be carried out since the presence of red blood cells, either intact or hemolyzed interferes with the signal generated by the chemical reaction performed by the test.

carried out by placing a blood sample in a centrifuge and centrifuging the sample for ten minutes at approximately 3,000 rpms. The serum obtained from this centrifuging step is then used to carry out the test, thus avoiding interferences from blood solids such as red blood cells.

An embodiment for chemical tests called dry reagent strips was developed first for urinalysis. Thereafter, vari us efforts to combine dry reagent strip technology in blood testing were started in the early 1950's. Notably, U.s. Patent No. 3,092,465

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discloses a reagent in a bibulous carrier with a superimp sed semipermeable coating to exclude the chemical and nonchemical interferences fr m red blood cells. The device, while performing analysis on whole blood, still required additi nal manipulations by the user, in the form of washing of excess blood after a specified time interval. Additionally, U.S. Patent Nos. 3,552,925 and 3,552,928 disclose the use of salts and amino acids to perform in-situ separation. U.S. Patent No. 4,477,575 discloses the use of a glass fiber matrix.

More recently, membranes have been employed in a variety of devices. These include devices disclosed in the following United States and foreign patents and publications: U.S. Patent Nos. 4,774,192 and 5,166,051; European Published Applications EP 0408222 A1, EP 0408223 A1, EP 0407800 A2 and EP 0388782; and PCT Published Applications Nos. WO 93/22453 and WC 90/10869. The use of the various membranes disclosed in the above patent documents operate on size exclusion principles, and several of these are limited by rates of capillary flow and do not completely eliminate interference from intact or hemolyzed red blood cells. Fresh red blood cells are elastic in nature and may pass through pores smaller than their nominal diameter. Hemolysis may occur on contact with some of the architectural or chemical components of the strips. Consequently, errors may be introduced into the measurement system.

U.S. Patent No. 5,104,619 discloses a disposable diagnostic system comprising a test card having a substantially flat body and a generally cylindrical reagent pad pocket formed in a central area of the flat body. A reagent chemistry pad is disposed in the pocket and a snap fit cover is received in the pocket and arranged over the pad to retain the pad in position. The device size and configuration allows for bar code graphics to be printed on the underneath side of th device. The bar code may contain lot specified data about the reagent chemistry,

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and is read by the meter during device insertion. This data may further contain critical parameters for the software algorithm within the meter electronics. U.S. Patent No. 5,139,685 also discloses a separation filter assembly having a snap fit lid. 5 - In this patent, glass fibers are utilized and maintained in a or compressed state under pressure code a reside bar. C

Accordingly, a need exists for an integrated system for assaying analytes and whole blood samples which are not affected by the chemical or physical interferences normally caused by red blood cells and other portions of whole blood.

## SUMMARY OF THE INVENTION

The present invention, in one form thereof, comprises a dry solid phase diagnostic test strip and system for the chemical. enzymatic, and/or immunological analysis of whole blood ...15 [2:50 analytes, comprising a reflectance photometer, a solid support strip, a porous detection zone member, a permeable spreading layer, an overlay sample receiving membrane containing an agent for the exclusion of intact red blood cells and a stripreceiving platform for positioning the strip inside the reflectance photometer. The detection area membrane may contain chemical, enzymatic, and/or immunological reagents that generate aspecific signals in the presence of a target analyte. agent, in contact with the overlay membrane, prevents passage and hemolysis of red blood cells while facilitating rapid transport and reaction of the plasma or serum portion of war and a dintroduced whole blood, samples, a polygon of a war

In addition, the present invention, in one form thereof, comprises a reflectance photometer which utilizes test strips that are color coded for test differentiation. For example, a blue strip may indicate a glucose test, whereas a red strip may indicate a cholesterol test. These colors are then divided into shades such as 64 shades to 64 lot numbers of glucose strips. The photom ter includes a separate optical read

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head that determines the color and shade of the base of the test strip device as the strip is inserted into the photometric instrument. The shade is converted into a lot number ranging from 1 to 64. The instrument also has a memory module (preferably an electrically erasable programmable read-only memory) that has a corresponding lot number to the shade of the strip to ensure lot number verification. The instrument then compares the inserted memory module programmed lot number to ensure that it is the same lot number as the test strip. If the strip lot number does not match the memory module lot number, the test is not performed, and the user is instructed to insert the correct memory module.

The lot number verification allows for the automated coding of lot numbers so that the user does not need to enter a lot code for each vial of strips. This prevents the running of the incorrect, old, or expired lot number tests in the instrument.

The "plug-in memory" of the module includes the lot number of the test strip, the expiration date, and the performance criteria for the actual strip measurement. The performance criteria include the wavelength, measurement algorithm, and unreacted density qualifications necessary for a valid test result.

The optoelectronic measurements of the chemistry test reaction on and in a surface enhances the dynamic range of the dry phase test. Algorithms that read at different wavelengths at different times in the chemistry reaction can extend the dynamic range of the test system. This is particularly applicable when using multiple chromophores in a single measurement system. The early portion of a chemistry could be read at the peak wavelength of a reaction, while the later portion or darker or more dens portion of color development c uld be read at a wavelength not near the peak of the color development. In addition, different chromoph res may respond in

a more linear manner in different portions of the dynamic range of the chemistry. Manipulation of these two data points can significantly increase the dynamic range (in mg/dl) of a chemistry reaction. Compression and American

The optoelectronic measurement of the chemistry test reaction on and in a surface reduces error due to orientation f the surface to be read to the instrument. Multiple wavelengths and different angles are used to correct possible problems in positioning the strip in the instrument. If the detector is at "O" angle and the emitters of the same or different wavelengths are at different angles (e.g., one at 40° and one at 50°), the tilting of a surface will positively contribute to one reading while it will contribute in a negative manner to the other reading thus it is able to cancel the error presented by the 15 angle presentation of the surface. These same measurement methods can be used to eliminate interferences from substances such as bilirubin and others.

The optoelectronic measurements of the chemistry test reaction on and in the surface enhance the stability of timed and untimed dry phase chemistry reaction. Algorithms are used to determine the "end point" of a chemistry. In other words, measurements can be done at similar or dissimilar wavelengths to predict, the stable portion or end point of a chemistry. kinetic measurements are made, the kinetic readings can be 25 subjected to an algorithm to determine that the rate is slow enough to declare the extrapolate chemistry is at an end or completion. When known standards are run and predicted by this pseudo-endpoint, the same measuring criteria can be applied to unknowns to determine the "endpoint" of the test reaction.

The use of colored or shaded visual indicators in the instrument enhance the interpretation of test results. colored bar graph is used to aid the user in knowing when the ស្រីស្តាមេរីស្រីស្តេខ ស ស្ត្រី ខេត្ត ខេត្ user test results are in a normal or safe range. Out of range Condition of the second

colors such as orange for caution and red for danger are used
when results ar outside the green "safe" range. This is
particularly useful to new testers who are not familiar with the
number scale of the different test results. A voice module can
also be used to warn the user of unsafe results or peration of
the instrument system to make the system usable by the visually
impaired by providing, for example, a sound beep for each unit
of glucose during a glucose test.

## BRIEF DESCRIPTION OF THE DRAWINGS

in accordance with an embodiment of the present invention;

Fig. 2 is an exploded perspective view of the plastic test strip of present invention in its unlocked position;

Fig. 3 is a perspective view of the plastic strip of Fig. 2

15 in its locked position; and

Fig. 4 is a sectional view of the plastic strip;

the reflectance photometer of the present invention;

Fig. 6 is a graph plotting sample size, elapsed test time
and percentage of reflectance illustrating how endpoint
determinations may be utilized to speed chemistry measurement.

## DESCRIPTION OF THE PREFERRED EMBODIMENT

the diagnostic chemistry measurement device 10 for dry solid

phase chemical, enzymatic, immunological assay of whole blood or
sera analytes is made up of an injection molded carrier test

strip 20 in which several porous and nonporous materials
containing chemicals and reactants are contained for the purpose

of generating a detectable signal in the presence of certain

analytes. The test strip 12 is inserted into a reflectance
photometer. The reaction material layer on the test strip 12 is
held in intimate noncompressed contact with a whole blo d

s paration layer in the absence of adhesives f r the purpose of

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providing a liquid sample free of red blood cells to the reaction layer or layers.

## Holder

The holder test strip 12 of this invention acts as holder for the different layers of the test reaction system. It provides a convenient handle as well as a mechanism for placing test strip 12 into an instrument 10 for the reading of the density changes of the feaction layers. As shown in Fig. 2 test strip 12 includes an elongate body 16 preferably formed by injection molding. Elongated body 16 includes a first end portion 18 and a second end portion 20.000 A hinged portion 22 is located between first and second and end portions 18 and 20 so that first end 18 is foldable over elongated body 16 into contact with second end 20.000 and 20.0000 and 20.00000 and 20.0000 and 20.0000 and 20.0000 and 20.0000 and

As shown in Fig. 2 first end portion 18 includes a opening 24 while second end portion 20 includes a complementary spaced opening 26. When first end portion 18 is folded over body 16 each opening 24 and 26 are aligned. In its folded position as shown in Fig. 3 opening 24 in test strip 12 defines an area for depositing a body fluid sample while opening 26 defines an area in which optoelectronic measurements of chemistry test reactions are conducted.

Test strip 12 further includes an adhesiveless carrier layer 14 formed from, for example, three particular layers. In a standard diagnostic test strip, carrier layer 14 may include a disbursement layer 28, formed of for example woven materials such as polyester or cotton, for rapid and even disbursement of body fluid along carrier layer 14. Beneath that may be included a separating layer 30 constructed of known materials such as shown in Table IX infra, that, when exposed to a sample liquid, may separate analyt and analyte disrupting elements such as rad blood cells from whole blood. This action would permit the serum analytes to pass through separating layer 30 while

preventing r d bl od cells r other analyte disrupting elements from passing thr ugh. The last layer shown in Fig. 2 is that of the test reaction membrane 32 on which the dry chemicals and reactants are contained for generating a visible signal in the presence of serum analytes. Molded carrier body 16 serves as a support for the reacting and nonreacting layers 28, 30 and 32 which may be formed from papers, membranes and deles materials.

The test strip holder 12 positions the different layer materials 28, 31, 32 within the holder the correct X, Y, and Z axis positions. Carrier layer 14 made up, for example, the one of well had been a consider to disbursement separating and test reaction layers 28, 30 and 32 are held in noncompressed adhesiveless locations by first end portion 18 folding over to second end portion 20. This may be accomplished in a number of different ways. The preferred way of noncompressingly holding carrier layer is of an upstanding annular rim 34 may help locate the carrier layer 14 within test strip 12. Additionally, small upstanding protuberances 36 along second end portion 20, radially located away from opening 26 prevent movement of carrier layer 14. The purpose of both annular rim 34 and small upstanding protuberances 36 is to hold the layers of carrier layer 14 without compression between opening 24 and opening 26, thereby preventing pooling of any sample within carrier layer 14. This consideration of noncompression of the carrier layer 14 is of greater importance when larger numbers of layers are utilized. The positioning f a carrier layer 14 without adhesives or compression allows for efficient transport of sample and reactants contained in the system and test strip 12. Annular rim 34 or alternatively other areas of test strip 12 may include sawtooth protrusions to increase flow rate through carrier layer 14...

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Test strip 12 includes a 1 cking mechanism to prevent any unlocking of front end porti n 18 from its folded p sition over elongated body 16. As shown in Fig. 2, one type of locking

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mechanism may include a plurality of upwardly extending tabs or 古りまち カラー (のない projections 38 that interfit or lock into corresponding openings 10 4 2 1 1 2 40 in first end portion 18. When first end portion 18 is folded tian takan di salah d 72..... to second end portion 20, lock projections 38 will interfit and snap lock within openings 40. Other types of one way locking ្រុកទៅ ស្រុកស្រួស សារីធិសាស . . . mechanisms may also be used, such as snap rivets.

A STATE OF THE STATE OF THE PROPERTY OF THE STATE OF THE More than one test reaction system can be housed in a test ក្រុមស្រុក ស្រុក ស្រុកស្នាល់ ស្ត្រាស់ ស្រុកស្នាប់ ស្រុកបានបើក្រុមបែ strip 12. A second set of holes 24, and 26 may be included in ್ , ಸರ್ಕಣಗ ಬ್ರತ್ತ test strip 12 so that two tests may be run at once.

The described holding mechanism allows for the rapid separation of whole blood into its liquid and solid components. It also allows sample volumes as low 2.0 microliters to be used in dry phase chemistry reactions. Test strip 12 allows the use of several reaction and non-reaction layers. A typical holder could contain from 1 to 8 layers of material with thicknesses 一直的第三人称形式 化二氯磺基甲二二甲基苯甲甲基 . . . . . from approximately 0.002 inches to 0.007 inches, for example.

Chemicals and materials are employed to allow for the treatment of samples such as whole blood, which will allow the whole blood sample to be separated without disrupting the red blood cells while rapidly moving the liquid portion of the whole blood sample to one or more reaction sites in the holder, normally on a test reaction membrane 32. These chemicals can be 12 50 composed of polymeric and nonpolymeric substances that are dried onto one or more surfaces of the materials contained in the device holder. Additionally, light metal salts of elements such as Potassium, Lithium, Sodium, and Calcium may be utilized to treat red blood cells before and during the separation process. The materials which may be used in the holder for treatment by or containment of these chemicals can be composed of woven, nonwoven, napped, or flocked materials.

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#### **Analytes**

A wide variety of analytes can be determined by using the disclosed apparatus. Examples are given in tables I and II,

Further, given the small size and robust nature of the reagent strips and instrumentation, analyses need not be limited to traditional clinical laboratory settings. The device of the present invention is also simple enough to be used by people swith minimal or no chemical or medical technology training. This advantage allows use at home, or by mobile health care delivery people. Examples of this are diabetics that must and) monitomethemselves for glucose and ketone bodies, patients on home dialysis who would benefit by monitoring of urea nitrogen and people endeavoring to lower their cholesterol levels.

15. Further, by combining several different reagants on a single support, a panel of tests may be done. Examples of this would be abliver panel consisting of ALT, AST, Alkaline Phosphates. A diabetic panel might consist of glucose, beta hydroxybutryrate and glycated hemoglobin. A coagulation panel might consist of Prothrombin time, ACTT, and ACT.

#### FAMILIES OF ANALYTES BY STRUCTURE

#### Table I

; ; · · Examples ;
glucose, lactose, galactose
urea nitrogen, creatinine, uric acid
cholesterol, triglycerides, LDL, HDL
ALT, AST, Alkaline Phosphatase, CPK, CK-MB
NCG, LII
theophylline
cocaine, marijuana, barbiturates, salicylates
Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , Li <sup>+</sup> , CO <sup>2</sup>
infectious disease, forensic applicati ns, genetic dis rders

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## FAMILIES OF ANALYTES BY DISEASE

#### Table II

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Disease

Examples

Diabetes	glucose, beta hydroxybutyrate, hemoglobin					
Liver problems	ALT, AST, bilirubin					
Acidosis/Alkalosi	po <sub>2</sub> , pco <sub>2</sub> , pH					
Hypertension:	Nat, Kt. It will be the I'm said					
Nutritional status	Ca <sup>++</sup> , Mg <sup>++</sup> , 2n <sup>++</sup> , traca minerals					

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#### to Examples of some and the element of element grantial

Strange & " towar to

The following illustrative examples theach various combinations of buffers and yes and stabilizers and other reactive and functional components which may be combined by a person and shaving ordinary skill in the lambsinto the system test reaction

diagnostic reagents.

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## Example #1 1000 com a construction is a construction of the constr

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#### TABLE III

Amount Amount Available from Ingredient & Function Sigma Chemicals, reactant 25,000 % Glucose Oxidase St. Louis, MO Sigma Chemicals, 75,000 reactant ----Peroxidase Sta Louis, MO . Discel ್ರಾರ್ಮಗಳ ಉಗ್ರಾಕ್ಷ Dow-Corning, 0.10ml Silwet 7500 surfactant. Midland, MI ISP, Linden, NJ 0.50gms ... PVP K 30 ..... enzyme legovi el: 50 17 13 stabilizers Aldrich Chemical, Buffers Hapris 1.25gms at Citric Acid Milwaukee, WI system yothir i Dow-Corning, ( 0.10ml Buffer Sodium citrate Midland, MI system----Aldrich Chemical, antifoam . .. 1.00gms DOW 1520 Milwaukee, WI

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4 AAP	chromophore	0.25gms	Aldrich Chemical, Milwaukee, WI
3,5 DCHBS	chromophore	0.25mgs	Boehringer Mannheim
Distilled H20	solvent	QS to 100ml	

Preparation: Approximately 50ml of distilled H20 was placed in a beaker on a stirring plate. A magnetic bar was added and the ingredients added sequentially after the previous gradient was dissolved and dispersed. After all ingredients were added the volume was adjusted to 100ml of distilled  ${\rm H}_2{\rm O}$ .

Example 200 and to the state of the

Triglycerides measuring system

TRIGLYCERIDES + H2O CHOLESTEROL ESTERASE GLYCEROL + FREE FATTY ACIDS GLYCEROL + ATP GLYCEROL KIHASE L - ALPHA - GLYCEROPHOSPHATE + H2O2

10 H<sub>2</sub>O<sup>2</sup> + 4=AMINOANTIPYRINE + DCHBS PEROXIDASE QUINONEIMINE CHROMOPHORE

#### TABLE IV

Ingredient	Function	Amount	Available from
Cholesterol esterase		15,000 units	Shinko-American, N.Y., N.Y.
glycerol kinase	reactant	5,000 units	Shinko-American, N.Y., N.Y.
glycerophosphate oxidase	reactant	5,000 units	Shinko-American, N.Y., N.Y.
peroxidase	reactant	5,000 units	Shinko-American, N.Y., N.Y.
4 AAP	chromogen	1.00gm	Aldrich
121	chromogen	-0.25gm	Boehringer Mannheim
MES	buffer	2.50gm	Research Organics
PVP K30	stabilizer	0.50gm	ISP
glucose Plant?	filler	2.50gm	Sigma
triton X-100	surfactant	0.10gm	Boehringer Mannheim
Distilled H <sub>2</sub> 0_	s lv nt	QS to 100ml	

Preparation: Same as example #1

Example 3

Cholesterol measuring system (all amounts approximate) 

	Ingredient	Function	Amount	Available from
	Cholesterol Oxidase	reactant	10,000	Shinko-American, N.Y., N.Y.
	- 48 S 3 7 7 3 4 4	표도를 받아난 3년	i re hands	W.1., W.1.
	cholesterol esterase	reactant b	537,000 <sub>025</sub> -	Shinko-American, N.Y.,N.Y.
a a seleta e		buffer	750 ml របស្រិច មទាទា ភពៈ	Dow-Corning,
	B.S.A.	surfactant	15 gm	Aldrich Chemical,
	peroxidase	reactant	170,000 BAT	Shinko-American,
¥	DOSS	surfactant	an 2.01 gms/	Boehringer Mannheim
सर्वे विकास	sucrose	stabilizer	1.0 gms	Sigma Chemicals,
i	THE	chromogen	10.0 gms	Aldrich Chemical,
- 1 ( 65%) AND ST	Distilled H <sub>2</sub> O	solvent	QS to 100 ml	į

Preparation: same as example #1 And the Table Total

Alternatively, the chromogen may be prepared in an organic solvent matrix and treated as a first or 2nd application to the

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# 5 TABLE VI

Ingredient			Available from
Acetone/methanol 1:1	solvent	100ml	Aldrich
Tetramethyl benezidine	solvent chromogen	1.00gm	Biosynth Inc., Chicago, IL

Example 4 Page 1 Section 19 Company 1 Company

Blood Urea Nitrogen Measuring System 

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Ingredient	Function
Urease	reactant
H <sub>2</sub> 0	solvent
Bcomthymol blue	chromogen
PVP K90	film former
Fructose	filler

Preparation: Same as experiment #1.

Language Allendary

Sometimen to be a first to be

ក្នុង 30 និក្សាមហុខ បាល់១ ការពី១១១ ១០ 

Types of Indicators

Chromogenic substrate provide the control of the co

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Leuco dyes commence and the commence of the co

Oxidative couplers

Benzidene Derivatives

Fluorescent labels

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Dye releasing system

#### Table IX

Separation mechanisms used in dry reagents

<sup>1</sup> Chemical	Physical	Hechanical
Dextran	hydrophilic polymers	centrifuge
sugars	porous latex films	filters
lectin	polymer & swelling agent	filters & pressure
•	membranes	membranes & differential pressure
PEG/polyacrylate	microfiber cloth	wedge shape
thrombin	napped cloth	
gels	sintered p r us matrix	
coagulants	density gradient	
agglutinating - agents	glass fibers	. 6. 1

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amine polymers	hollow fibers	 	
trivalent cations	membrane	. 1.3	

#### Spectrophotometer

The present invention also includes use of a spectrophotometric device 10 for determining the density of the color reaction on and in the membrane surface of the test reaction layer 32 within test strip 12. Photometric device 10 as shown in Fig. 1 includes a hand-held housing 50 for containing electronic control circuitry for operating the aforementioned tests. In the embodiment shown in Fig. 1, a test strip holding region 52 is located above three light detectors or sensors 54 each disposed within a port 56. During test operation, a test strip 12 is inserted into holding region 52 so that test strip openings 26 are located adjacent ports 56. Light sensors may take a reading from light reflected from the exposed test reaction membrane layer 32 or from test strip 12 itself to determine its color.

Housing 50 further includes a specialized display device, such as a liquid crystal display 58. Display 58 is utilized for relating test results and other information to the user. In particular, a color scale 60 is used to facilitate interpretation of test results operating concurrently with digital display segments, 62. Additional display segments on display 58 include a test wait indicator segment 64 to inform the user to wait while device 10 is performing the selected tests, and a test name segment 66 which the unit determined from the type of test strip 12 inserted.

Color scale 60 may easily by constructed by a plurality of shaded or colored segments arranged adjacent each ther to f rm a bar graph like indicator. Electrically controllable segments 68 are oriented over the color or shaded segments so that when segments 68 are activated segments 68 become dark, preventing

certain colored or shaded segments 60 from being visualized or viewed. Segments 68 that are not activated permit the underlying colored or shaded segments of color scale 60 to be visualized. In this way it is possible for an electronic 5 control to permit only a single colored or shaded segment to be viewed thereby communicating test results. 1.3

A possible result range spectrum for color scale indication segments may include particular colors with particular test result meanings such as:

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Very high result danger, RED

with the second transfer than high result danger, RED to the second second

high result caution, YELLOW

high normal result, GREEN was a second of the

15 green and the normal regult, GREEN, see and borg and

The second result, GREEN, which is a subject to the second result.

low result caution, YELLOW

low result caution, YELLOW

very low result danger, RED

Color scale 60 permits an unsophisticated user to instantly visually determine, in one embodiment, if a test result is normal (a green segment visualized), slightly abnormal (a yellow segment visualized) or dangerous high or low result (a red segment visualized) ... Alternatively, if a color liquid crystal 25. display is jutilized, the electronic control for test unit 10 may directly indicate a colored segment, rather than covering all but one colored segment.

A suitable instrument, such as a diffuse reflectance 30 - spectrophotometer 10 with appropriate software, can be made to automatically read reflectance at certain points in time, calculate the rate of reflectance change, and by using calibrati n factors and software, output the level of analyte in

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the fluid tested. The electronic control mechanism of photometric unit 10 is shown in schematic form in Fig. 5. One or more light sources 70, for example high intensity light emitting diodes (LED) are disposed in housing 50 to illuminate 5 test strip 12 as shown by arrows 72. A light detector or sensor 54, for example a photo transistor, is able to take a reading of light reflected either from the surface of test strip 12 or from ; its associated test reaction membrane 32: Light source 70 and light sensor 54 can be adapted to generate or respond to particular wavelengths of Profit for the state

> Sensor 70 transmits a signal to an amplifier 74 as is known in the art. One type of amplifter available for use is, for example, a linear integrated circuit which converts the phototransistor current to a voltage signal.

> Appropriate electronic circuitry is utilized to take the output of amplifier 747 normally a sample and hold unit 76, and transfer the signal to an analog-to-digital converter 78. Analog-to-digital converter takes the analog voltage output from the sample and hold unit 76 and converts it to, for example a 16 bit binary digital number upon command of a microprocessor/ microcontroller unit 80% macrosque alate no co-

Preferably an electronic microprocessor/microcontroller 80 utilizing digital integrated circuitry is used to time selected tests, read signals, and together with associated programs and (25 / data memory 82), calculate and store reflectivity valves and And In the calculate analyte levels from the stored data years of

Additional information for particular tests may be stored in a removable EEPROM unit 84 operably connected to microprocessor/microcontroller 80 30 EEFROM unit 84 is an interchangeable plugain memory module containing measurement parameters, software, calibration data, and reagent recognition data for particular test strips 112 and Additionally, EEPROM unit 84 contains the shelf life data and identity verification

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information for particular production runs or lots of test strips 12. A strips of the second strips of the sec

Automated lot coding is d ne by the color coding the plastic material used to make the test strip holder 12. The color used in test strip holder 12 preferably has 16 different densities that can be distinguished by at least one of the wavelengths used in the optical sensor head 54 of instrument 10. Condens of For instance the dynamic range of the toreflectances of the set rank . Astrip holder color could be as follows to determine the 10 to the different shades of color density:

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in the consistency of the fill became with this properties with the fill out to its ends

As the strips 12 are inserted into device 10, the instrument 011.3 1.0 detects a change in the measurement area. This change indicates that a strip 12 has been inserted into the instrument 10. As The green and a green was the 1.398 F. F. B. the instrument detects the insertion of a test strip 12, it The and for building as by two reads the densities of at least one of the LED's and calculates runin marakiyisan jeda j the lot number by the above table. Instrument 10 then goes to the EEPROM port connected to microprocessor / microcontroller 80 ຕາມຂອງເປັນສະເຕະ ລອດດ ທີ່ຕາ ເ which has an EEPROM unit 84 inserted. Instrument 10 checks to additioned to the child the manner of the see that the EEPROM preselected lot number is the same as lot The state of the s number of test strip 12 that had been inserted into the instrument. If the lot numbers are the same for test strip 12 and EEPROM 84, the instrument downloads the information contained in the EEPROM and proceeds with the test analysis.

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The instrument 10 reads the density of the unreacted strip to assure quality of the strip before the test is initiated, if quality is passed then the instrument instructs the user to gapply a sample. To the error of a findament the

Assample is then applied and instrument 10 begins a was the proper amount of sample was applied to the test strip. When the instrument has determined that enough sample has been applied, it then goes into another cycle to measure the end of the chemistry reaction. end of the chemistry reaction has coccurred? then the instrument measures the final density and compares it to a measurement algorithm stored in EEPROMe unit 84. This measurement algorithm Gad be3 then determines the concentration of the test to be measured by comparing the measured density (darkness) of the color formed and comparing this density number to a table of values through the use of an algorithm stored in the EEPROM unit 84.

After a particular test strip is selected and placed in the unit, a sample, normally a whole blood sample from a fingertip or from a pipiter tip (which could have gotten its sample from a tube of blood as in a laboratory type situation) is applied to the sample application spot, opening 24, on test strip 12. A dispersement layer 28 causes the sample to quickly spread over the entire area of carrier layer 14. The separation layer 30 of the test strip spot is allowed to separate out the solids (red a (4) 13 a 3227 1 324 1 11 12 . 13 blood cells and other analyte disrupting elements) from the ការស ស ប្រើ ដូច ស្សាន្ធិមានគេមិ ការ។ នៅស liquid (plasma or sera or other analyte containing portion). The separated fluid, i.e the plasma, sera, or other analyte 15 Bert St. 1885 containing portions, moves to the test reaction membrane layer 32 below the separation membrane 30. The above fluid migrati n causes the reactants (analytes such as glucose) in the sample to come into contact with the reactants in test reaction membrane layer 32. is then it is the matter, the ship that it is the big the

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Analytes/fluid contacts reagent layer reaction 32 and initiates an appearance or disappearance f color, depending on its particular reaction. The above presentation of analyte to the reaction layer 32 causes the desired reaction to cour. 5 This reaction causes a color change that can be detected both visually and by the instrument. The color change is then converted into a digital result on the instrument LCD as described above. A comparison color chart can be used to with a visually determine a reaction quantity scale as in litmus paper. 10 2000 COART Instrument 10 can use different wavelengths at different density portions of the reaction to maximize the dynamic range of the chemistry and the limits of the instrument at a particular wavelength.

The "end-point" of the reaction is defined as a point where 15 there appears to be no change or a very small change in density. That is, the chemistry changes color proportional to the concentration of the reactance that has come into contact with the reactance materials in the test pad (membrane). This small amount of change can be a change per time period. An example 20 would be as per the graph in Fig. 6. Detailed information used to generate this graph is that the changes per 5 second time period during the beginning of the test reaction would be greater than 5% reflectance per 5 second time period. When this change is less than 1% reflectance per time period it can be said that the reaction is complete or at an endpoint. The instrument stores this percentage reflectance at this time and uses as above to determine the concentration of the analyte tested for in the test strip.

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The Kubelka-Monk equation of K/S=(1-reflectance) divided by (2 x reflectance) can be used to linearize the percentage reflectance values. This linearization simplifies the algorithm necessary to calculate results. This pseudo endpoint chemistry allows a more stable read time, which in turn allows for a more

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repr ducible answer. Pseudo endpoints; also permit a more rapid assay to be performed. Certain other glucose monitoring systems incorporate pre-determined timing circuit. This pseudo endpoint allows for a different method to be used in measuring chemistry reactions, provided one can determine the endpoint of the chemistry by as method, other than stiming as 12 1,000

Multiple wavelengths are used to enhance the dynamic range of a chemistry. This is particularly useful when one uses a multiple chromophore indicator systems as do some of the above mentioned chemistries of Early sportions or those concentrations of a test such as glucose can use approad range indicator such as TMB to increase sensitivity in the downto mid range of the chemistry. When the test concentration is higher or the . And the reaction fasters and different chromophore is focused upon to 15 15 at adetermine more dynamic range than the previous chromophore. Age of This Hallows one to expands the dynamic range by two differents. methods, and in the first one is add to not send men int

One can also use wavelengths on the peak for more dynamic range and wavelengthshoff the "peak" absorbance of the test system to enhance or reduce dynamic range and also to enhance or reduce the "pseudo endpoint" algorithms. Manipulation of these ... of four factors, chromophore Agachromophore (Bashwaye length 1 and |wavelength 2 can allow cone to better | define the | pseudo endgreater point" algorithm and also allow one to goptimize the dynamic 25 mil range of the chemistry which in turn allows for increased sensitivity throughout the chemistry reaction range with greater ing the expression. The data of a set assertable for evaluate as above.

> Multiple wavelengths can also be used with different angles of emission to correct possible problems in positioning the strip in the instrument, with the detector is at "0" angle and the emitters of the same or different wavelengths are at different angels (one at 40% and one at 50°) the tilting of a surface will positively contribut to one reading while the

other contributes in a negative manner thus cancelling the error presented by the angle presentati n of the surface. These same measurements methods can be used to eliminate interferences from substanc s such as bilirubin and others. When the angle of light incidence is increased from improper positioning of a chemistry read surface to the instrument optics, errors of both gloss and angularity are introduced into the measuring system and can give false low readings.

#### Examples

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- 10 1. Indicators and chromogens advantageously used in combination
  - a. wide range pH test

Bromothymol blue and methyl red covers pH range of 5 through 9

- b. 4 amino antipyrine + 3,5 dichlorohydroxybenzene sulfonate (4AAP+3,5 DCHBS)
  - c. TMB+Chromotropic acid
  - d. Syringaldazine + Vanillin Azine
- 2. Color coding for test and lot identification
  - a. blues, 16 different shades (density)
- 20 b. reds, 16 different shades (density)
  - c. greens, 16 different shades (density)
  - d. yellows, 16 different shades (density)
  - e. oranges, 16 different shades (density)
  - f. browns, 16 different shades (density)
  - g. magentas, 16 different shades (density)
    - h. light blues, 16 different shades (density)
    - light reds, 16 different shades (density)
    - light greens, 16 different shades (density)
    - k. light browns, 16 different shades (density)
- 30 l. light magentas, 16 different shades (density)
  - m. cyan, 16 different shades (density)

#### light cyan, 16 different shades (density) n. light o ಸ್ವಾನ ಈ ಸ್ಥಿತ ಪ್ರಭಾವದ ಮಾಡುತ್ತಿಗೆ ಕಾರಣ ಮ grade A Color & Color

ing the second of the second o It will be appreciated that the foregoing is presented by way of illustration only, and not by way of any limitation, and that various alternatives and modifications may be made to the There is the state of the state

illustrated embodiment without departing from the spirit and scope of the invention.

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WHAT IS CLAIMED IS:

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1. A diagn stic test strip for use in an analyzer for measuring analyte in a sample, said test strip c mprising:

an elongate body including a first end, a second end, and a hinged portion between said first and second ends, said first end being foldable over said body, said first end and said second end each having an opening that are aligned when said first end is folded; and

an adhesiveless carrier layer disposed without compression between said first end and said body whereby sample communicated to said carrier layer is prevented from pooling within said carrier layer.

- 2. The test strip of Claim 1 in which said carrier layer includes a separating layer that when exposed to a whole blood sample excludes red blood cells from passing therethrough while allowing the liquid portion of the whole blood sample to pass therethrough.
- 3. The test strip of Claim 1 having a carrier layer utilizing samples in the range of 2.Oul to 10.Oul to generate a reaction to accurately test a selected analyte.
- 4. The test strip of Claim 1 in which said carrier layer includes:
- a separating layer that when exposed to a sample liquid having both analytes and analyte disrupting elements said separating layer excludes said analyte disrupting elements from passing therethrough while allowing the analyte portion of the sample liquid to pass therethrough; and
- a test reaction membrane adjacent said separating layer that creates a gradient color dependant on the concentration of selected analytes in the analyte portion that had passed through said separating layer.
  - 5. The test strip of Claim 1 in which said carrier layer

includes a spreading layer over said separating layer to cause sample to substantially evenly enter said separating layer.

- 6. Th test strip of Claim 1 in which said carrier layer may test more than one analyte at one time.
- 7. The test strip of Claim 1 in which said body includes a locking means lock together said first end and said body.
- 8. A diagnostic test strip for use in an analyzer for measuring analyte in a sample, said test strip comprising:

an elongate body including a first end, a second end, and a hinged portion between said first and second ends, said first end being foldable over said body, said first end and said second end each having an opening that are aligned when said first end is folded;

an adhesiveless carrier layer disposed between said

braid recta a connection dend novel printings a safe of

first end and said body of said carrier layer whereby the

which reconstanted printing rect also leads the descriptions are the

10 accuracy of measured analytes is increased; and the state of the st

non-compressive means holding said carrier layer in place between said first end and said body whereby pooling of sample within said carrier is prevented.

- 9. The test strip of Claim 8 in which said non-compressive means comprise protrusions to locate said carrier layer in place whereby said carrier layer is maintained in known locations along the X, Y and Z axis.
- compressive means comprise sawtooth protrusions to locate said carrier layer in place whereby said carrier layer is maintained in known locations along the X, Y and Z axis.
- layer is treated with light metal salts to reduce red blood cells in the sample.
  - 12. The test strip of Claim 8 in which said first end folds over said carrier layer and locks to said body causing the layers of said carrier layer to be in adjacent c ntact without

adhesives or compression whereby efficient separation f red blood cells from plasma in whole bl od samples.

an pening one of which on said first end the other n said second end so that when said first end folds into contact with said body, said tab interfits with said opening to lock said first end with said body.

that have solded A chemistry measurement system comprising:

a test instrument with a light source and light

an elongate body including a first end, a second end, and a hinged portion between said first and second ends, said first end being foldable over said body, said first end and said second end each having an opening that are aligned when said first end is folded, said test strip having an adhesiveless carrier layer disposed without compression between said first end and said body, said opening adapted to receive said sample; an electronic control for computing particular test results on light incident on said light sensor that was reflected from said test strip; and

15 displaysmeans for displaying said test results.

- 15. The measurement system of Claim 14 in which a plurality of test strips are utilized for particular chemical tests, said test strips color coded for identification of which said particular chemical test said test strip is operable.
  - 16. The measurement system of Claim 15 in which a plurality of test strips are utilized for particular chemical tests, said test strips color coded for identification of said particular chemical test for which said test strip is operable and lot designator, said light sensor sensing said col r of said test strip when said strip is inserted into said test instrument and sending a coded signal to said electronic control, said

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electronic control determining the type of test and lot designator of inserted test strip and denying test operation when said lot designator is not within predefined limits.

- 17. A chemistry measurement system of Claim 16 in which said system tests for more than one analyte with a single test strip. Burnay of as well as with at
  - 18. A chemistry measurement system comprising: a test instrument, with a light source and light Sensor: A (2) | a - 110 deembraam; desc 3

a color coded diagnostic test strip for use in analyzing a sample, said strip having an elongate body including a first end, a second end, and anhinged portions between said first and second ends; said first end being foldable over said body, said first endoand said second end teach having an opening The manufacturare aligned; when maid, first mend mis shoulded, said test strip 10 having an carrier layer disposed without compression between said first end and said body, said first end opening adapted t preceive said sample; on Team base the book track book to a

an electronic control for computing particular test results on light incident on said light sensor that was reflected from said test strip, said control determining from said color of said test strip if said test strip is from a , particular production lot, said control operating said test operation only if said test strip is from a preselected ្រុកសន្តិការ នេះ production (lotterand) នេះ នេះ២០០ នេត្តនៃយន នេះមេនា នៃដែន នេះ មាន

- 20 displaying said test results if said test is conducted? whoseve diseases as a di
- Application 19. A chemistry measurement system comprising: a test instrument with a light source and light sensor, said light source emitting light at multiple angles and multiple wavelengths; graff birt is on as
  - a diagnostic test strip for use in analyzing a sample, said test strip comprising an elongate body including a first

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end, a second end, and a hinged portion between said first and second ends, said first end being f ldable over said body, said test strip having an adhesiveless carrier layer disposed without compression between said first end and said body;

an electronic control for c mputing particular test results on light incident on said light sensor that was reflected from said test strip; and

FLEWERING AND FIRE Ordisplay: means: for displaying said test results.

- 20. The chemistry measurement system of Claim 19 in which said electronic control includes a removable erasable programmable read only memory unit containing lot number data and expiration data for particularly chemical tests.
  - 21. A liquid crystal display matrix for a hand-held chemistry measuring system, said display matrix comprising:
  - a display screen having a plurality of shaded segments arranged adjacent each other;
  - a plurality of controllable segments disposed within said screen oriented over said shaded segments, said controllable segments preventing visualization of said shaded segments when activated and permitting visualization of said shaded segments when deactivated whereby results from said chemistry measuring system are communicated by visualizing selected shaded segments.
  - 22. The liquid crystal display of Claim 21 in which said shaded segments are aligned in a line forming a substantial bar graph indicator.
  - 23. The liquid crystal display of Claim 21 in which said shaded segments are colored to indicate selected results from said blood chemistry measuring system.
  - 24. A method of testing analyte in a sample comprising the steps of :

providing a chemistry measurement system having a light sensor, test display, colored diagn stic test strips for

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		adhesiveless	carrier	layer	attached	without	compression	to	ваіс
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predetermined test; a second with the

- 10. The contract depositing a test sample on the carrier layer of the selected test strip; the contract contract the contract of the selected test strip; the contract the contract test strip; the contract test selected test strip; the contract test selected test selec
- - predetermined test; and we now the brown of conduct the displaying test results on estimatest display.
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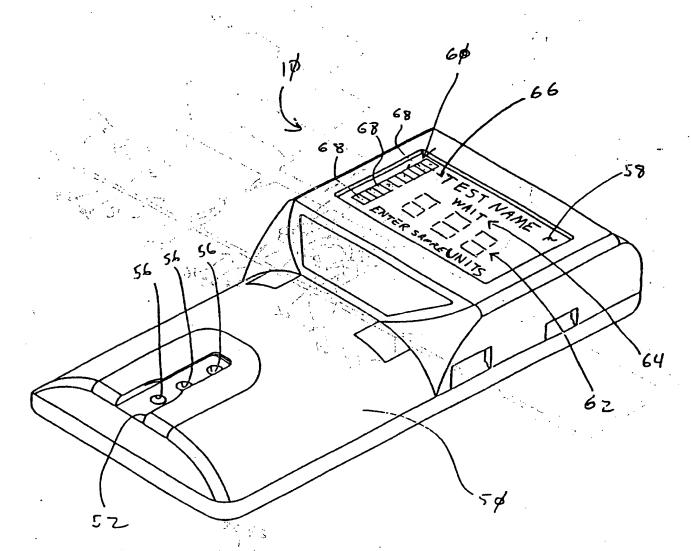
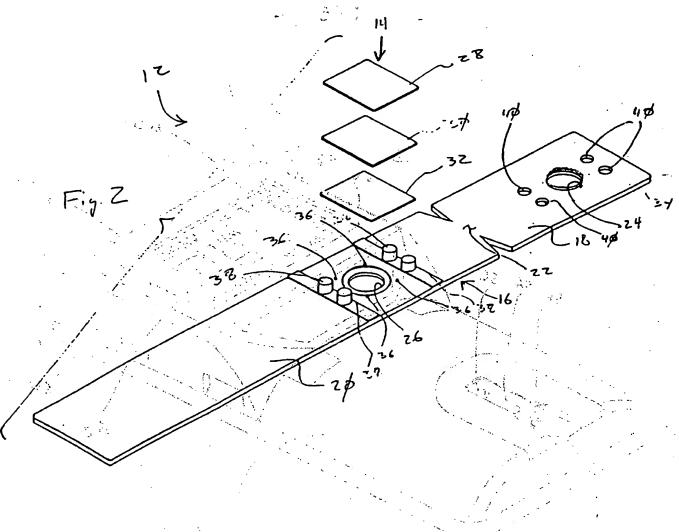


Fig I



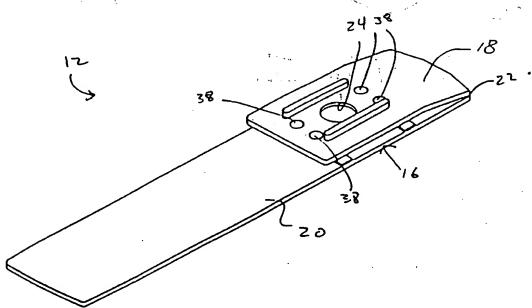
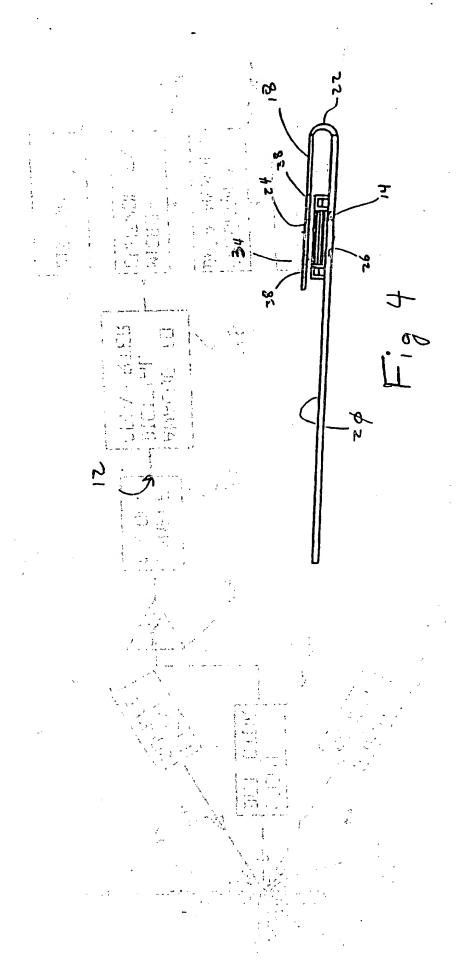
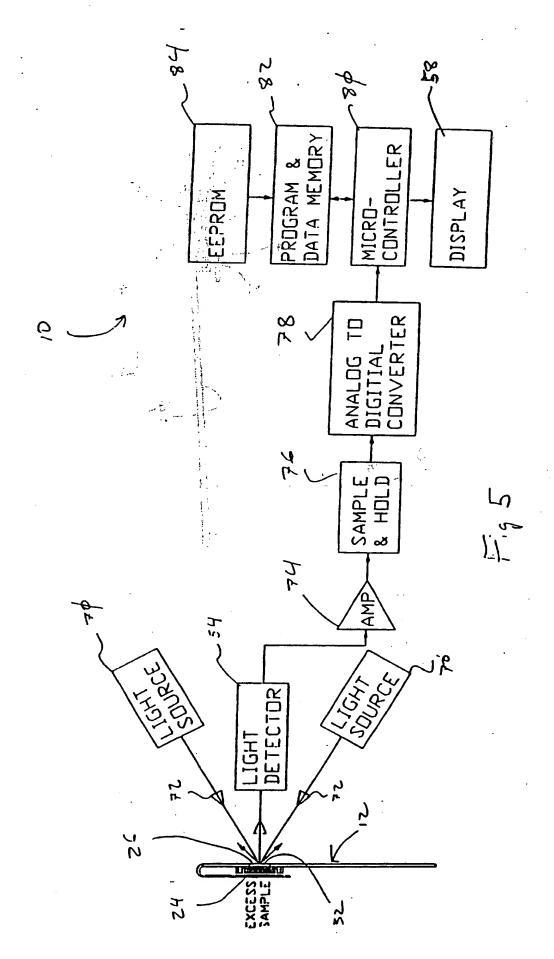


Fig. 3





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FIGURE 6 SHALL BE
CONSIDERED NON-EXISTENT
(See Article 14(2))



#### WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



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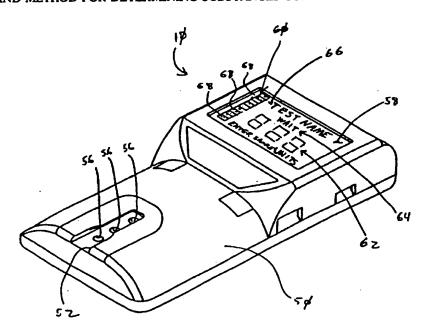
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(57) Abstract

An apparatus for the optoelectronic evaluation of test paper strips for use in the detection of certain analytes in blood or other body fluids. The test strip comprises an elongated plastic part including a hinged porti n to all w a first portion to be folded over a sec nd portion. A series of layers of test strips are disposed between the folded-over portions of the test strip. The step strip is configured such that the chemistry layers are placed in c ntacting engagement with one another, but not compressing one another. A reflectance ph tometer is provided and includes vari us features, including a lot number reader wherein if the test strip does n t match the memory module, a test is not performed, and the user is instructed to insert a correct memory module.

#### FOR THE PURPOSES OF INFORMATION ONLY

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PCT/US 95/12550

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/52 G01N21/84

G02F1/133

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 6 GOIN GOZF

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Special categories of cited documents:	T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the		
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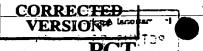
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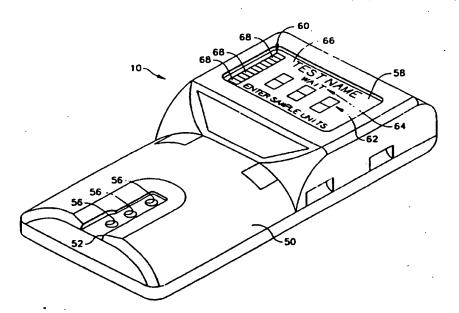
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#### (57) Abstract

An apparatus for the optoelectronic evaluation f test paper strips for use in the detection of certain analytes in blood or other body fluids. The test strip comprises an elongated plastic part including a hinged portion to allow a first portion to be folded over a second portion. A series of layers of test strips are disposed between the folded-over portions of the test strip. The step strip is configured such that the chemistry layers are placed in contacting engagement with one another, but not compressing one another. A reflectance photometer is provided and includes various features, including a lot number reader wherein if the test strip does not match the memory module, a test is not performed, and the user is instructed to insert a correct memory module.

<sup>• (</sup>Referred to in PCT Gazette No. 42/1996, Section II)

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# APPARATUS AND METHOD FOR DETERMINING SUBSTANCES CONTAINED IN A BODY FLUID

#### BACKGROUND OF THE INVENTION

The present invention relates generally to an assay system for biological and nonbiological fluids. More particularly, the present invention relates to an apparatus for separating serum or plasma from particulate matter and then optoelectronically evaluating the serum or plasma in order to measure analytes within the serum.

It has long been desirable to utilize devices that can be used for on-site testing of blood products. Particularly important is the analysis of body fluids from humans and animals to diagnose disease, monitor the course of therapy, or determine the presence of illicit drugs. Commonly, the analytical methods used to carry out these objects are performed on blood samples.

Clinical chemists have a preference for working with serum over plasma and plasma over whole blood because of the clarity of the sample matrix and the lack of interfering substances from the solid portion of the blood. In order to facilitate analysis, a separation step must be carried out since the presence of red blood cells, either intact or hemolyzed interferes with the signal generated by the chemical reaction performed by the test.

Conventionally, the separation of blood components has been carried out by placing a blood sample in a centrifuge and centrifuging the sample for ten minutes at approximately 3,000 rpms. The serum obtained from this centrifuging step is then used to carry out the test, thus avoiding interferences from blood solids such as red blood cells.

An embodiment for chemical tests called dry reagent strips was developed first for urinalysis. Thereafter, various efforts to combine dry reagent strip techn logy in bl od testing were started in the early 1950's. Notably, U.s. Patent N . 3,092,465

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discloses a reagent in a bibulous carrier with a superimposed esemipermeable coating to exclude the chemical and nonchemical interferences from red blood cells. The device, while performing analysis on whole blood, still required additional manipulations by the user, in the form of washing f excess blood after a specified time interval. Additionally, U.S. Patent Nos. 3,552,925 and 3,552,928 disclose the use of salts and amino acids to perform in-situ separation. U.S. Patent No. with the areas of 4,477,575 discloses the was of anglass fiber matrix.

. More recently, amembranes have been employed in a variety of devices These include devices disclosed in the following United States and foreign patents and publications: U.S. Patent Nos. 4,774,192 and 5,166,051; European Published Applications EP 0408222 A1, EP 0408223 A1, EP 0407800 A2 and EP 0388782; and PCT Published Applications Nos. WO. 93/22453 and WO 90/10869. The use of the various membranes disclosed in the above patent documents operate on size exclusion principles, and several of these are limited by rates of capillary flow and do not completely eliminate interference from intact or hemolyzed red 20 blood cells. Fresh red blood cells are elastic in nature and may pass through pores smaller than their nominal diameter. Hemolysis may occurson contact with some of the architectural or chemical components of the strips. Consequently, errors may be introduced into the measurement system.

25 . . . . U.S. Patent No. 5,104,619 discloses a disposable diagnostic system comprising a test-card having a substantially flat body and a generally cylindrical reagent pad pocket formed in a central area of the flat body. A reagent chemistry pad is disposed in the pocket and a snap fit cover is received in the 30 Jan appocket and arranged over the pad to retain the pad in position. The device size and configuration allows for bar code graphics to be printed on the underneath sid of the device. The bar code may contain lot specified data about the reagent chemistry,

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and, is read by the meter during device insertion. This data may further contain critical parameters for the software algorithm within the meter electronics. U.S. Patent No. 5,139,685 also discloses asseparation filter assembly having a snap fit lid. 5 . In this patent, glass fibers are utilized and maintained in a The compressed state under pressure Pour Court and Court of the court sales is a selection shocordingly, as need exists for an integrated system for assaying analytes and whole blood samples which are not affected by the chemical or physical interferences normally caused by red 10 blood cells and other portions of whole blood. Summary Soft The Invention by a SUMMARY SOF STREET INVENTION BY SECTION 1985 greathermetion; sindone formsthereof, comprises a dry solid phase diagnostic test strip and system for the chemical, www.secomenzymatic, and/or ammunological analysis of whole blood 15 garagamalytes, comprising a reflectance photometer, a solid support Sand large estrip, a porous detection zone member, as permeable spreading service layer; an overlay sample receiving membrane containing an agent ofor the exclusion of intactored blood cells and a stripreceiving platform for positioning the strip inside the reflectance photometers. The detection area membrane may contain 20 . chemical, enzymatic, and/or immunological reagents that generate specific signals in the presence of a target analyte. The agent, in contact with the overlay membrane, prevents passage and hemolysis of red blood cells while facilitating rapid 25 25 transport and reaction of the plasma or serum portion of The will wintroduced whole: blood samples: https://www.committer.com/ 4 61 4 6 Inhaddition, the present invention, in one form thereof, 22 8 % comprises a reflectance photometer which utilizes test strips that are color-coded for test differentiation. For example, a

blue strip may indicate a glucose test, whereas a red strip may indicate a cholester 1 test. These c'1 recare then divided int shades such as 64 shades fiblue equal t 64 lot numbers of gluc se strips. The ph tometer includes a separate optical read

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head that determines the color and shade of the base of the test strip device as the strip is inserted int the ph t metric instrument. The shade is converted int a lot number ranging from 1 to 64. The instrum nt also has a mem ry m dule (preferably an electrically erasable programmable read-nly memory) that has a corresponding lot number to the shade of the strip to ensure lot number verification. The instrument then compares the inserted memory module programmed lot number to ensure that it is the same lot number as the test strip. If the strip lot number does not match the memory module lot number, the test is not performed, and the user is instructed to insert the correct memory module.

The lot number verification allows for the automated coding of lot numbers so that the user does not need to enter a lot code for each vial of strips. This prevents the running of the incorrect, old, or expired lot number tests in the instrument.

The "plug-in memory" of the module includes the lot number of the test strip, the expiration date, and the performance criteria for the actual strip measurement. The performance criteria include the wavelength, measurement algorithm, and unreacted density qualifications necessary for a valid test result.

The optoelectronic measurements of the chamistry test reaction on and in a surface enhances the dynamic range of the dry phase test. Algorithms that read at different wavelengths at different times in the chemistry reaction can extend the dynamic range of the test system. This is particularly applicable when using multiple chromophores in a single measurement system. The early portion of a chemistry could be read at the peak wavelength of a reaction, while the later portion or darker or more dense portion of color development could be read at a wavelength not near the peak f the color development. In additi n, different chromophores may respond in

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> a mor linear manner in different portions of the dynamic range f the chemistry. Manipulation of these two data points can significantly increase the dynamic range (in mg/dl) of a chemistry reaction. 81 62 5 WHT

The optoelectronic measurement of the chemistry test . We have a definition of T such that if T is T , T in Treaction on and in a surface reduces error due to orientation of the Art of Aug. of the term and the transport of the surface to be read to the instrument. Multiple wavelengths and different angles are used to correct possible problems in positioning the strip in the instrument. If the detector is at "O" angle and the emitters of the same or different wavelengths are at different angles (e.g., one at 40° and one at 50°), the tilting of a surface will positively contribute to one reading while it will contribute in a negative manner to the other reading thus it is able to cancel the error presented by the angle presentation of the surface. These same measurement of prantient odd trias and risks and risks and risks and risks and risks and risks. methods can be used to eliminate interferences from substances with while feed recover the last upon the last plant of the control of the con such as bilirubin and others.

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The optoelectronic measurements of the chemistry test reaction on and in the surface enhance the stability of timed and untimed dry phase chemistry reaction. Algorithms are used to determine the "end point" of a chemistry. In other words, measurements can be done at similar or dissimilar wavelengths to predict the stable portion or end point of a chemistry. If kinetic measurements are made, the kinetic readings can be subjected to an algorithm to determine that the rate is slow enough to declare the extrapolate chemistry is at an end or ្រ ទូកាំល សុខិរី មេដ សុខគ.វ ។ ៤៤ ប៊ុន) completion. When known standards are run and predicted by this 化化二甲醇 特别研究 电相流 显示 经部分 pseudo-endpoint, the same measuring criteria can be applied to unknowns to determine the "endpoint" of the test reaction. med z du bar

The use of colored or shaded visual indicators in the Mark Starten Dayley 2007 instrument enhance the interpretation of test results. A ်ကို နေတီလိုက်တွင် လည်းသည်သည် သွေးသောကြာသည်။ လူနေတွင် ရေးသည်သည့် colored bar graph is used to aid the user in knowing when the The wind of Topics sink of the contract of the user test results are in a normal or saf range. Out of range

colors such as orange for caution and red for danger are used when results ar outside the green "safe" range. This is particularly useful to new testers who are not familiar with the number scale of the different test results. A voice m dule can also be used to warm the user of unsafe results or peration of the instrument system to make the system usable by the visually impaired by providing, for example, a sound beep for each unit ent to promote of glucose during a glucose test.

BRIEF DESCRIPTION OF THE DRAWINGS 10 Fig. 1 is a perspective view of the reflectance photometer in accordance with an embodiment of the present invention;

Fig. 2 is an exploded perspective view of the plastic test strip of present invention in its unlocked position;

Fig. 3 is a perspective view of the plastic strip of Fig. 2

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15 in its locked position; and the second was

Valuation Fig. 4 is a sectional view of the plastic strip;

215 TOVE 3 THE Pigg 5, is a block diagram schematic of one embodiment of the reflectance photometer of the present invention;

Fig. 6 is a graph plotting sample size, elapsed test time 20 and percentage of reflectance illustrating how endpoint determinations may be utilized to speed chemistry measurement.

# DESCRIPTION OF THE PREFERRED EMBODIMENT

In accordance with the embodiment of the present invention, the diagnostic chemistry measurement device 10 for dry solid phase chemical, enzymatic, immunological assay of whole blood or sera analytes is made up of an injection molded carrier test strip 20 in which several porous and nonporous materials containing chemicals and reactants are contained for the purpose of generating a detectable signal in the presence of certain 30 analytes. The test strip 12 is inserted into a reflectance photometer. The reaction material layer on the test strip 12 is held in intimate noncompressed contact with a whole blood s paration layer in the absenc of adhesives for the purpose of

providing a liquid sample free of red blood cells t the reaction layer or layers. ស្តីរដ្ឋា ទៅក្នុង **រាជ្រុ**ង ស្ត្

# Holder and Miles and the Holder

The holder test strip 12 of this invention acts as holder 5 for the different layers of the test reaction system. It provides a convenient handle as well as a mechanism for placing test strip 12 into an instrument 10 for the reading of the density changes of the reaction layers. As shown in Fig. 2 test strip 12 includes an elongate body 16 preferably formed by injection molding. Elongated body 16 includes a first end portion 18 and a second end portion 20. A hinged portion 22 is located between first and second and end portions 18 and 20 so that first end 18 is foldable over elongated body 16 into contact with second end 20.

As shown in Fig. 2 first end portion 18 includes a opening 24 while second end portion 20 includes a complementary spaced opening 26. When first end portion is is folded over body 16, each opening 24 and 26 are aligned. In its folded position as shown in Fig. 3 opening 24 in test strip 12 defines an area for 20 depositing a body fluid sample while opening 26 defines an area in which optoelectronic measurements of chemistry test reactions are conducted. .... 233. 1981 1981

Test strip 12 further includes an adhesiveless carrier layer 14 formed from, for example, three particular layers. In 25 a standard diagnostic test strip, carrier layer 14 may include a disbursement layer 28, formed of for example woven materials such as polyester or cotton, for rapid and even disbursement of body fluid along carrier layer 14: Beneath that may be included a separating layer 30 constructed of known materials such as shown in Table IX infra, that, when exposed to a sample liquid, may separate analyte and analyte disrupting elements such as red blood cells from whole bl od? This action would permit the serum analytes to pass thr ugh separating layer 30 while

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preventing red blood cells or other analyte disrupting elements fr m passing through. The last layer shown in Fig. 2 is that f the test reaction membrane 32 on which the dry chemicals and reactants are contained for generating a visible signal in the presence of serum analytes. Molded carrier body 16 serv s as a support for the reacting and nonreacting layers 28, 30 and 32 which may be formed from papers, membranes and deles materials.

The test strip holder 12 positions the different layer materials 28, 31, 32 within the holder the correct X, Y, and Z reduction of the second axis positions. Carrier layer 14 made up, for example, the was beautiful out the course disbursement separating and test reaction layers 28, 30 and 32 in our work were between egener are held in noncompressed adhesiveless locations by first end Commence of the second second portion 18 folding over to second end portion 20. This may be nyacam <u>kang pe</u>ninjanah kang dalam accomplished in a number of different ways. The preferred way of noncompressingly holding carrier layer is of an upstanding annular rim 34 may help locate the carrier layer 14 within test strip 12. Additionally, small upstanding protuberances 36 al ng second end portion 20, radially located away from opening 26 prevent movement of carrier layer 14. The purpose of both annular rim 34 and small upstanding protuberances 36 is to hold the layers of carrier layer 14 without compression between opening 24 and opening 26, thereby preventing pooling of any sample within carrier layer 14. This consideration of noncompression of the carrier layer 14 is of greater importance when larger numbers of layers are utilized. The positioning of a carrier layer 14 without adhesives or compression allows f r efficient transport of sample and reactants contained in the system and test strip 12. Annular rim 34 or alternatively other areas of test strip 12 may include sawtooth protrusions to increase flow rate through carrier layer 14...

Test strip 12 includes a locking mechanism to prevent any unlocking of front end p rtion 18 from its folded p sition over elongated body 16. As shown in Fig. 2, ne type f locking

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mechanism may include a plurality of upwardly extending tabs or pr jections 38 that interfit or lock into corresponding openings  $t + \alpha$  . 40 in first end portion 18. When first end portion 18 is folded March Brown Land to second end porti n 20, lock projections 38 will interfit and a lather the stage of the course of the course snap lock within openings 40. Other types of one way locking mechanisms may also be used, such as snap rivets.

More than one test reaction system can be housed in a test ंतुं भारत हर रहा है। हा ले स्तु जल के देखा उट्टी अला पुरान पर के ती strip 12. A second set of holes 24, and 26 may be included in test strip 12 so that two tests may be run at once.

The described holding mechanism allows for the rapid separation of whole blood into its liquid and solid components. disturbement bepayairig 193 tour 8 40 % 5 % It also allows sample volumes as low 2.0 microliters to be used in dry phase chemistry reactions. Test strip 12 allows the use of several reaction and non-reaction layers. A typical holder personal control of division of any and control and the trial 15 could contain from 1 to 8 layers of material with thicknesses from approximately 0.002 inches to 0.007 inches, for example.

Chemicals and materials are employed to allow for the かい えい しょうキテチがいひかぶ treatment of samples such as whole blood, which will allow the whole blood sample to be separated without disrupting the red blood cells while rapidly moving the liquid portion of the whole blood sample to one or more reaction sites in the holder, normally on a test reaction membrane 32. These chemicals can be composed of polymeric and nonpolymeric substances that are dried onto one or more surfaces of the materials contained in the 5 device holder. Additionally, light metal salts of elements such as Potassium, Lithium, Sodium, and Calcium may be utilized to treat red blood cells before and during the separation process. The materials which may be used in the holder for treatment by or containment of these chemicals can be composed of woven, nonwoven, napped, or flocked materials.

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หลางสาราช (สาราช (สาราช (สาราช (สาราช <del>โดยสาราช (สาราช (สาราช (สาราช (สาราช (สาราช (สาราช (สาราช (สาราช (สาราช</del>

大学 化电子电子 A wide variety of analytes can be det rmined by using the Examples are given in tables I and II, disclosed apparatus.

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Further, given the small size and robust nature of the reagent strips and instrumentation, analyses need not be limited to traditional clinical laboratory settings. The device of the present invention is also simple enough to be used by people with minimal or no chemical or medical technology training. This advantage allows use at home, or by mobile health care delivery people. Examples of this are diabetics that must monitor themselves for glucose and ketone bodies, patients on home dialysis who would benefit by monitoring of urea nitrogen and people endeavoring to lower their cholesterol levels.

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Further, by combining several different reagents on a single support, a panel of tests may be done. Examples of this would be a liver panel consisting of ALT, AST, Alkaline Phosphates. A diabetic panel might consist of glucose, beta hydroxybutryrate and glycated hemoglobin. A coagulation panel might consist of Prothrombin time, ACTT, and ACT.

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# FAMILIES OF ANALYTES BY STRUCTURE.

#### Table I

Fomily	Examples
Carbohydrate	glucose, lactose, galactose
Nitrogen Moiety	urea nitrogen, creatinine, uric acid
Lipid	cholesterol, triglycerides, LDL, HDL
	ALT, AST, Alkaline Phosphatase, CPK, CK-MB
Hormone	HCG, LH
Therapeutic Drugs	theophyllina
Drugs of abuse	cocaine, marijuana, barbiturates, salicylates
Electrolyte	Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , Li <sup>+</sup> , CO <sup>2</sup>
Nucleic Acids	infecti us disease, for naic applications, genetic disorders

### FAMILIES OF ANALYTES BY DISEASE 建铁 化电流设置工程机 建铁 化建筑 化环状二烷烷基

# Disease The reserve to the reserve to

,	Diabetes	glucose, beta hydroxybutyrate, hemoglobin				
and the state of the second	7 1	"1c				
A STATE OF STATE OF	Liver problems	ALT, AST, bilirubin				
.: 100 .przeż (	Acidosis/Alkalosi	pc2, pco2, pH to other second				
కున్నా క కంతో టీర	Hypertension	Ne to Rational stock from the state of the				
i verentri i	Nutritional status	Catt, Mgtt, Zntt, trace minerals				
		CH OTE HOLDER BUSHINGS 6.425 CF				

## THE Examples of the state and another the expect grewnful

The following illustrative examples teach various combinations of buffers, dyes, stabilizers and other reactive and functional components which may be combined by a person 5 having ordinary skills in the art into the system test reaction වෙන්න එය අතුරුව<mark>ැඩිසිමෙම ස</mark>ොස්ට්රි පති අතුර පෝස්තාල ලිට විකාරකයේ කිය සහසමුල්ම පටද ය

Table IX gives various types of dyes and indicators used in property of agnostic reagents. The second of the second se

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128 July 12

Glucose measuring system ( 2000) 1983 10

#### TABLE III

Ingredient -	. Function	Amount Y	Available from
Glucose Oxidase	reactanto	25,000 10	Sigma Chemicals, St. Louis, MO
Peroxidase	reactant	75.000	Sigma Chemicals, St. Louis, MO
511wet 7500 n	surfactant	0.10ml	Dow-Corning, Midland, MI
PVP K. 30	enzyme stabilizer:	- 0.50gms	Ten Ti-i-
Citric Acid	Buffer st	- 1.25cms	Aldrich Chemical, Milwaukee, WI
Sodium citrate	Buffer system	; 0.10ml	D w-Corning, Midland, MI
DOW 1520	antifoam	- 1.00gms	Aldrich Chemical, Milwaukee, WI

4 AAP	chromophor	0.25gms	Aldrich Chemical, Milwaukee, WI
3,5 DCHBS	chromophor	0.25mgs	Boehringer Mannheim
Distilled H20	solvent	QS to 100ml	

1 ,, 1 Preparation: Approximately 50ml of distilled H2O was placed in a beaker on a stirring plate. A magnetic bar was added and the The second se has been ingredients added sequentially after the previous gradient was ...... dissolved and dispersed..... After all ingredients were added the prilar Liberton volume was adjusted to 100ml of distilled H20. and the second s

Example 2000.000 Single Control of Control o

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Triglycerides measuring system

TRIGLYCERIDES + H,O CHOLESTEROL ESTERAGE GLYCEROL + FREE FATTY ACIDS GLYCEROL + ATP GLYCEROX KIRASE L - ALPHA - GLYCEROPHOSPHATE + H2O2 H202 + 4-AMINOANTIPYRINE + DCHBS. PEROXIDASE QUINONEIMINE CHROMOPHORE

E.IV to definition

TABLE IV

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Ingredient	Function	Amount	Available from
Cholesterol esterase	reactant	15,000 units	Shinko-American, N.Y., N.Y.
glycerol kinase	reactant	5,000 units	Shinko-American, N.Y., N.Y.
glycerophosphate oxidase	reactant	5,000 units	Shinko-American, N.Y., N.Y
peroxidase	reactant	5,000 units	Shinko-American, N.Y., N.Y.
4 AAP	chromogen	1.00gm	Aldrich
3, 5 DCIIBS	chromogen	0.25gm	Boehringer Mannheim
MES	buffer	2.50gm	Research Organics
PVP K30	stabilizer	0.50gm	ISP.
glucose name?	filler	2.50gm	Sigma
triton X-100	surfactant	0.10gm	Boehringer Mannheim
Distilled H <sub>2</sub> 0	solvent	QS to 100ml	

Preparation: Same as example #1

Ch lesterol measuring system (all amounts approximate) COMPANY TO SELECTION OF THE PROPERTY OF THE PR

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### TABLE V

2.	Ingredient	Function	Amount	Available from
-	Cholesterol Oxidase	reactant	10,000	Shinko-American, N.Y., N.Y.
	cholesterol esterase	1 .	1	Shinko-American, N.Y., N.Y.
	1	buffer	750 ml	Dow-Corning,
	B.S.A.	surfactant	15 gm	Aldrich Chemical,
	peroxidase	reactant	170,000\$ 785	Shinko-American,
a Artii a Loota l	DOSS W	080	2001 <b>70 00 gms</b> u (	Boehringer Mannheim
		stabilizer		Sigma Chemicals,
,	TMB Thirdenseries TMBASS. e.e.	chromogen		Aldrich Chemical,
		solvent	QS to 100 ml	

Preparation: "same as: example #1 and the second of the second s

Alternatively, the chromogen may be prepared in an organic solvent matrix and treated as a first or 2nd application to the membrane or paper. THE RESERVE AS TELL BY THE

# TABLE VI

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4	Ingredient	Function 1	Amount	Available from
-	Acetone/methanol 1:1	solvent	100ml	Aldrich
	Tetramethyl benezidine	solvent chromogen	1.00gm	Biosynth Inc., Chicago, IL

330-2123-37 577

#### Example 4 manage of a comment of the comment o

Blood Urea Nitrogen Measuring System n gestra i de la companya de la comp

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Ingredient Function	
Urease Wanging Mile	reactant
H <sub>2</sub> 0	solvent
Bcomthymol blue	chromogen
PVP K90	film former
Pructose	filler

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Preparation: Same as experiment /1. BIT WILLIAMSON SON THE BUILD CONTROL OF THE SON OF THE SON OF

Table VIII Manualisma a ventina i i had I en e i

Types of Indicators

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 $\mathbf{5}=\{\mathbf{g}_{1},\ldots,\mathbf{g}_{n}\}_{n=1}^{\infty}$   $\mathbf{Redox}_{\mathbf{G}}\mathbf{x}_{n}$  because of an exception of the  $\mathbf{g}_{1}$ 

្សារក្រុក **Leuço dyes** (ភេឌ) ១៦ ១៩៩ ខេម្មកម្មជា មួនជា ១២៩៦ មិនប

who have the commendate Derivatives to the commendate of the comme

Pluorescent labels

Dye releasing system Table IX 10

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425 40 200

Separation mechanisms used in dry reagents

Chemical	Physical	Mechanical
pextran	hydrophilic polymers	centrifuge
sugars	porous latex films	filters
lectin	polymer & swelling agent	filters & pressur
lectin		membranes &
amino acids	Se tue alla e e e e e e e e e e e e e e e e e	differential pressure
	microfiber cloth	wedge shape
thrombin	napped cross	
gels	sintered porous matrix	
coagulants	density gradient	
agglutinating -	glass fibers	

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amine polymers -	hollow fibers	1
trivalent cations	membrane	(1) 4 (1)

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### <u>Spectrophotometer</u>

The present invention also includes use of a spectrophotometric device 10 for determining the density of the color reaction on and in the membrane surface of the test 1 " 1 reaction layer 32 within test strip 12. Photometric device 10 as shown in Fig. 1 includes a hand-held housing 50 for containing electronic control circuitry for operating the aforementioned tests. In the embodiment shown in Fig. 1, a test strip holding region 52 is located above three light detectors or sensors 54 each disposed within a port 56.7 During test operation, a test strip 12 is inserted into holding region 52 so that test strip openings 26 are located adjacent ports 56. Light sensors may take a reading from light reflected from the exposed test reaction membrane layer 32 or from test strip 12 itself to determine its color. ្នុងរាជធាននិយាសាសមា ប្រសិ

Housing 50 further includes a specialized display device, such as a liquid crystal display 58. Display 58 is utilized for relating test results and other information to the user. In particular, a color scale 60 is used to facilitate

20 interpretation of test results operating concurrently with digital display segments 62. Additional display segments on display 58 include a test wait indicator segment 64 to inform the user to wait while device 10 is performing the selected tests, and a test name segment 66 which the unit determined from the type of test strip 12 inserted.

Color scale 60 may easily by constructed by a plurality of shaded or colored segments arranged adjacent each other to form a bar graph like indicator. Electrically c ntr llable segments 68 are oriented over the color or shaded segments so that when segments 68 are activated segments 68 become dark, preventing

certain colored or shaded segments 60 from being visualized or view d. Segments 68 that are not activated permit the underlying col red or shaded segments of col r scale 60 to be visualized. In this way it is possible for an electronic control to permit only a single colored or shaded segment t be viewed thereby communicating test results.

A possible result range spectrum for color scale indication segments may include particular colors with particular test result meanings such as:

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high result caution, YELLOW

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normal result, GREEN to Control of the entire transfer of the control of the entire transfer of the control of

normal result, GREEN weight Legal to Sugden

low normal result, GREEN property of the second control of the property of the second control of the second co

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low result caution, YELLOW

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very low result danger, RED.

Color scale 60 permits an unsophisticated user to instantly visually determine, in one embodiment, if a test result is normal (a green segment visualized), slightly abnormal (a yellow segment visualized) or dangerous high or low result (a red segment visualized). Alternatively, if a color liquid crystal display is utilized, the electronic control for test unit 10 may directly indicate a colored segment, rather than covering all but one colored segment.

A suitable instrument, such as a diffuse reflectance spectrophotometer 10 with appropriate software, can be made to automatically read reflectance at certain points in time, calculate the rate of reflectance change, and by using calibrati n factors and software, output the level of analyte in

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the fluid tested. The electronic control mechanism of photometric unit 10 is shown in schematic form in Fig. 5. or more light sources 70, for example high intensity light emitting diodes (LED) are disposed in housing 50 to illuminate 5 test strip 12 as shown by arrows 72. A light detector or sensor 54, for example a photo transistor, is able to take a reading f light reflected either from the surface of test strip 12 or from in a lite associated test reaction membrane 32. Light source 70 and light sensor 54 can be adapted to generate or respond to particular wavelengths of light.

> Sensor 70 transmits a signal to an amplifier 74 as is kn wn in the art. One type of amplifier available for use is, for example, a linear integrated circuit which converts the phototransistor current to a voltage signal.

Appropriate electronic circuitry is utilized to take the output of amplifier 74, normally a sample and hold unit 76, and transfer the signal to an analog-to-digital converter 78. Analog-to-digital converter takes the analog voltage output from the sample and hold unit 76 and converts it to, for example a 16 bit binary digital number upon command of a microprocessor/ microcontroller unit 80. Microcontroller unit 80. Microcontroller unit 80.

Preferably an electronic microprocessor/microcontroller 80 utilizing digital integrated circuitry is used to time selected tests, read signals, and together with associated programs and 25 data memory 82, calculate and store reflectivity valves and calculate analyte levels from the stored data.

Additional information for particular tests may be stored in a removable EEPROM unit 84 operably connected to microprocessor/microcontroller 80. EEPROM unit 84 is an interchangeable plug-in memory module containing measurement parameters, software, calibration data, and reagent recognition data for particular test strips 12. Additionally, EEPRON unit 84 contains the shelf life data and identity verification

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strips:12.

Automated lot coding is die by the color coding the plastic material us die make the tist strip holder 12. The color used in test strip holder 12 preferably has 16 different densities that can be distinguished by at least one of the wavelengths used in the optical sensor head 54 of instrument 10. For instance the dynamic range of the treflectances of the strip holder color could be as follows to determine the different shades of color density:

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	Reflectance Reflectance Lot F Green LED Red LED	. :
	1.65 Comment of 30	
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٠.	40	3.01. 75.5
20	30	•
		•
	45 40 35	

35 As the strips 12 are inserted into device 10, the instrument detects a change in the measurement area. This change indicat s that a strip 12 has been inserted into the instrument 10. As the instrument detects the insertion of a test strip 12, it reads the densities of at least one of the LED's and calculates the lot number by the above table. Instrument 10 then goes to The same the self with a conthe EEPROM port connected to microprocessor / microcontroller 80 where the transfer of the state which has an EEPROM unit 84 inserted. Instrument 10 checks t The state of the s see that the EEPROM preselected lot number is the same as lot The state as east young need the state number of test strip 12 that had been inserted into the instrument. If the 1 t numbers are the same for test strip 12 and EEPROM 84, the instrument downloads the information contained in the EEPROM and pr ceeds with the test analysis.

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The instrument 10 reads the density; of the unreacted strip to assure quality f the strip before the test is initiated, if quality is passed then the instrument instructs the user to apply a sample.

measurement cycle to ensure that the proper amount of sample was applied to the test strip. When the instrument has determined that enough sample has been applied, it then goes into another cycle to measure the end of the chemistry reaction. When the end of the chemistry reaction has occurred, then the instrument measures the final density and compares it to a measurement algorithm stored in EEPROM unit 84. This measurement algorithm then determines the concentration of the test to be measured by comparing the measured density (darkness) of the color formed and comparing this density number to a table of values through the use of an algorithm stored in the EEPROM unit 84.

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After a particular test strip is selected and placed in the unit, a sample, normally a whole blood sample from a fingertip or from a pipiter tip (which could have gotten its sample from a tube of blood as in a laboratory type situation) is applied to the sample application spot, opening 24, on test strip 12. A dispersement layer 28 causes the sample to quickly spread over the entire area of carrier layer 14. The separation layer 30 f the test strip spot is allowed to separate out the solids (red blood cells and other analyte disrupting elements) from the e a salita la como transili Figura Salita liquid (plasma or sera or other analyte containing portion). of more as and more a court was The separated fluid, i.e the plasma, sera, or other analyte 7 B 18 1 1 2 of the 22 Timeself makes the containing portions, moves to the test reaction membrane layer 32 below the separation membrane 30. The above fluid migration ong Sing Minakapanang Pathologist ing Kali causes the reactants (analytes such as glucose) in the sample t come into contact with the reactants in test reacti n membrane titte at blir etter ombest gab gar 1 , layer 32.

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Analytes/fluid contacts reagent layer reaction 32 and initiates an appearance or disappearance of color, depending on its particular reaction. The above presentation of analyt to the reaction layer 32 causes the desired reaction to occur.

This reaction causes a color change that can be detected both visually and by the instrument. The color change is then converted into a digital result on the instrument LCD as described above. A comparison color chart can be used to visually determine a reaction quantity scale as in litmus paper.

Instrument 10 can use different wavelengths at different density portions of the reaction to maximize the dynamic range of the chemistry and the limits of the instrument at a particular wavelength.

The "end-point" of the reaction is defined as a point where there appears to be no change or a very small change in density. That is, the chemistry changes color proportional to the concentration of the reactance that has come into contact with the reactance materials in the test pad (membrane). This small amount of change can be a change per time period. An example would be as per the graph in Fig. 6. Detailed information used to generate this graph is that the changes per 5 second time period during the beginning of the test reaction would be greater than 5t reflectance per 5 second time period. When this change is less than 1t reflectance per time period it can be said that the reaction is complete or at an endpoint. The instrument stores this percentage reflectance at this time and uses as above to determine the concentration of the analyte tested for in the test strip.

The Kubelka-Monk equation of K/S=(1-reflectance)<sup>2</sup> divided by (2 x reflectance) can be used to linearize the percentage reflectance values. This linearization simplifies the algorithm necessary to calculate results. This pseudo endp int chemistry allows a m re stable read time, which in turn allows for a more

reproducible answer. Pseudo endpoints also permit a more rapid assay to be performed. Certain other glucose monitoring systems incorporate pre-d termined timing circuit. This pseudo endp int allows for a different method to be used in measuring chemistry reactions, provided one can determine the endpoint of the chemistry by a method other than timing.

Multiple wavelengths are used to enhance the dynamic range of a chemistry. This is particularly useful when one uses a multiple chromophore indicator system as do some of the above mentioned chemistries. Early portions or low concentrations of a test such as glucose can use a broad range indicator such as TMB to increase sensitivity in the low to mid range of the chemistry. When the test concentration is higher or the reaction faster, a different chromophore is focused upon to determine more dynamic range than the previous chromophore.

This allows one to expand the dynamic range by two different methods.

One can also use wavelengths on the peak for more dynamic range and wavelengths off the "peak" absorbance of the test

20 system to enhance or reduce dynamic range and also to enhance reduce the "pseudo endpoint" algorithms. Manipulation of these four factors, chromophore A, chromophore B, wavelength 1 and wavelength 2 can allow one to better define the "pseudo endpoint" algorithm and also allow one to optimize the dynamic range of the chemistry which in turn allows for increased sensitivity throughout the chemistry reaction range with greater precision.

Multiple wavelengths can also be used with different angles of emission to correct possible problems in positioning the strip in the instrument. If the detector is at "0" angle and the emitters of the same or different wavelengths are at different angels (one at 40° and one at 50°) the tilting of a surface will positively contribute to one reading while the

other contributes in a negative manner thus cancelling the error presented by the angle presentation of the surface. These same measurements methods can be used to eliminate interferences from substances such as bilirubin and others. When the angle of light incidence is increased from impr per positioning of a chemistry read surface to the instrument optics, errors of both gloss and angularity are introduced into the measuring system and can give false low readings.

#### Examples

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- 1. Indicators and chromogens advantageously used in combination
  - a. wide range pl test

Bromothymol blue and methyl red covers pil range of 5 through 9

- b. 4 amino antipyrine + 3,5 dichlorohydroxybenzene sulfonate (4AAP+3,5 DCHBS)
  - c. TMB+Chromotropic acid
  - d. Syringaldazine + Vanillin Azine
- 2. Color coding for test and lot identification
  - a. blues, 16 different shades (density)
  - reds, 16 different shades (density)
  - c. greens, 16 different shades (density)
  - d. yellows, 16 different shades (density)
  - e. oranges, 16 different shades (density)
  - f. browns, 16 different shades (density)
  - g. magentas, 16 different shades (density)
  - h. light blues, 16 different shades (density)
  - i. light reds, 16 different shades (density)
  - j. light greens, 16 different shades (density)
  - k. light browns, 16 different shades (density)
- light magentas, 16 different shades (density)
  - m. cyan, 16 different shades (density)

n. light eyan, 16 different shades (density)

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It will be appreciated that the foregoing is presented by way of illustration only, and n t by way of any limitation, and that various alternatives and modifications may be made to the illustrated embodiment without departing from the spirit and

scope of the invention.

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Fig. 1. So that are sets of the area of the control o

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en la companya di seriente de la companya de la co En la companya de la STATE OF WHAT IS CLAIMED IS:

1. A diagn stic test strip for use in an analyzer for measuring analyte in a sample, said test strip comprising:

an elongate body including a first end, a second end, and a hinged portion between said first and second ends, said first end being foldable over said body, said first end and said second end each having an opening that are aligned when said first end is folded; and

an adhesiveless carrier layer disposed without compression between said first end and said body whereby sample 10 communicated to said carrier layer is prevented from pooling within said carrier layer.

- 2. The test strip of Claim 1 in which said carrier layer includes a separating layer that when exposed to a whole blo d sample excludes red blood cells from passing therethrough while allowing the liquid portion of the whole blood sample to pass therethrough.
  - utilizing samples in the range of 2.Oul to 10.Oul to generat a reaction to accurately test a selected analyte.
- 4. The test strip of Claim 1 in which said carrier layer

a separating layer that when exposed to a sample liquid having both analytes and analyte disrupting elements said separating layer excludes said analyte disrupting elements from passing therethrough while allowing the analyte portion of the sample liquid to pass therethrough; and

layer that creates a gradient color dependant on the

concentration of selected analytes in the analyte portion that

had passed through said separating layer.

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5. The test strip of Claim 1 in which said carrier layer

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includes a spreading layer over said separating layer to cause sample to substantially evenly enter said separating layer.

- 6. The test strip f Claim 1 in which said carrier layer may test more than one analyte at ne time.
- 7. The test strip of Claim 1 in which said body includes a locking means lock together said first end and said body.
- measuring analyte in a sample, said test strip comprising:
  - and a hinged portion between said first and second ends, said

    first end being foldable over said body, said first end and said

    second end each having an opening that are aligned when said

    first end is folded; 12 to quara and and a
- an adhesiveless carrier layer disposed between said

non-compressive means holding said carrier layer in place between said first end and said body whereby pooling of sample within said carrier is prevented.

- 9. The test strip of Claim 8 in which said noncompressive means comprise protrusions to locate said carrier
  layer in place whereby said carrier layer is maintained in known
  locations along the X, Y and Z axis.
- 10. The test strip of Claim 8, in which said noncompressive means comprise sawtooth protrusions to locate said
  carrier layer in place whereby said carrier layer is maintained
  in known locations along the X . Y and Z axis.
  - layer is treated with light metal salts to reduce red blood cells in the sample.
    - 12. The test strip of Claim 8 in which said first end
      f lds over said carrier layer and 1 cks to said body causing the
      layers of said carrier layer t be in adjacent contact without

adhesives or compression whereby efficient separation of red

blo d cells from plasma in whole blood samples.

13. The test strip of Claim 1 further comprising a tab and an pening one of which on said first end the other in said second end so that when said first ind folds int contact with said body, said tab interfits with said opening to lock said

5 first end with said body.

the state of 14. TA chemistry measurement system comprising:

a test instrument with a light source and light

an elongatesbody including a first end, a second end, and a hinged portion between said first and second ends, said first end being foldable over said body, said first end and said second end each having an opening that are aligned when said first end is folded, said test strip having an adhesiveless carrier layer disposed without compression between said first end and said body, said opening adapted to receive said sample; an electronic control for computing particular test

results on light incident on said light sensor that was reflected from said test strip; and

15 display means for displaying said test results.

- 15. The measurement system of Claim 14 in which a plurality of test strips are utilized for particular chemical tests, said test strips color coded for identification of which said particular chemical test said test strip is operable.
  - plurality of test strips are utilized for particular chemical tests, said test strips color coded for identification of said particular chemical test for which said test strip is operable and 1 t designator, said light sensor sensing said color of said test strip when said strip is inserted into said test instrument and sending a coded signal t said electronic c atrol, said

electronic control determining the type of test and lot
designator of inserted test strip and denying test operation

10 when said lot designator is not within predefined limits.

17. A chemistry measurement system of Claim 16 in which
said system tests for more than one analyte with a single test
strip.

18. A chemistry measurement system comprising:

a test instrument with a light source and light
sensor;
sensor;

a color coded diagnostic test strip for use in

analyzing a sample said strip having an elongate body including
a first end, a second end, and a hinged portion between said
first and second ends, said first end being foldable over said
body, said first end and said second end each having an opening
that are aligned when said first end is folded, said test strip
having an carrier layer disposed without compression between
said first end and said body, said first end opening adapted t
receive said sample;

results on light incident on said light sensor that was

reflected from said test strip, said control determining from said color of said test strip if said test strip is from a particular production lot, said control operating said test operation only if said test strip is from a preselected production lot; and

a test instrument with a light source and light sensor, said light source emitting light at multiple angles and multiple wavelengths;

a diagnostic test strip f r use in analyzing a sample, said test strip comprising an elongate body including a first

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end, a second end, and a hinged portion between said first and sec nd ends, said first end being foldable ver said body, said test strip having an adhesiveless carrier layer disposed with ut compression between said first end and said b dy;

an electronic control for computing particular test results on light incident on said light sensor that was reflected from said test strip; and

display means for displaying said test results.

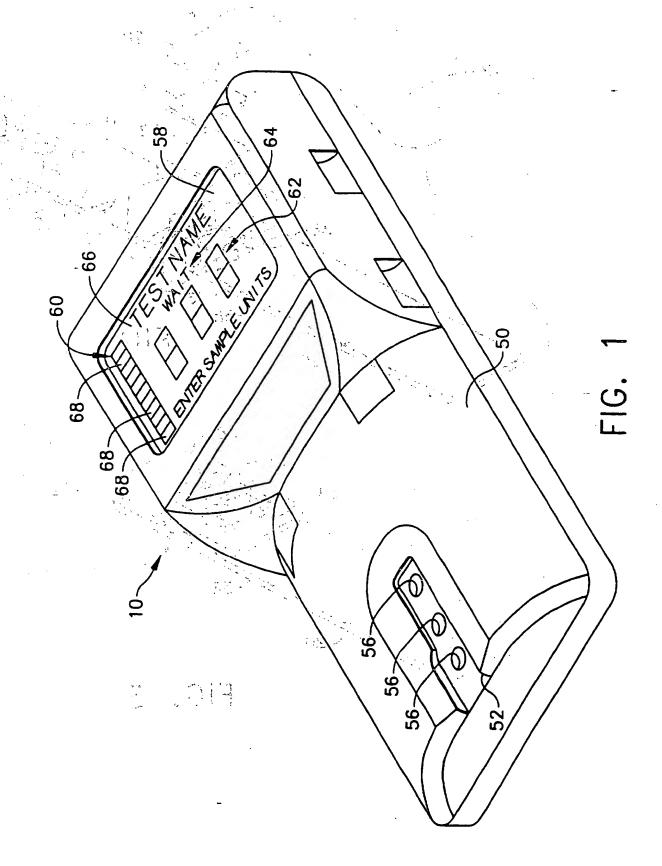
- 20. The chemistry measurement system of Claim 19 in which said electronic control includes a removable erasable programmable read only memory unit containing lot number data and expiration data for particularly chemical tests.
  - 21. A liquid crystal display matrix for a hand-held chemistry measuring system, said display matrix comprising:
  - a display screen having a plurality of shaded segments arranged adjacent each other;
  - a plurality of controllable segments disposed within said screen oriented over said shaded segments, said controllable segments preventing visualization of said shaded segments when activated and permitting visualization of said shaded segments when deactivated whereby results from said chemistry measuring system are communicated by visualizing selected shaded segments.
  - 22. The liquid crystal display of Claim 21 in which said shaded segments are aligned in a line forming a substantial bar graph indicator.
  - 23. The liquid crystal display of Claim 21 in which said shaded segments are colored to indicate selected results from said blood chemistry measuring system.
  - 24. A method of testing analyte in a sample comprising the steps of :

providing a chemistry measurement system having a light sensor, test display, colored diagnostic test strips f r

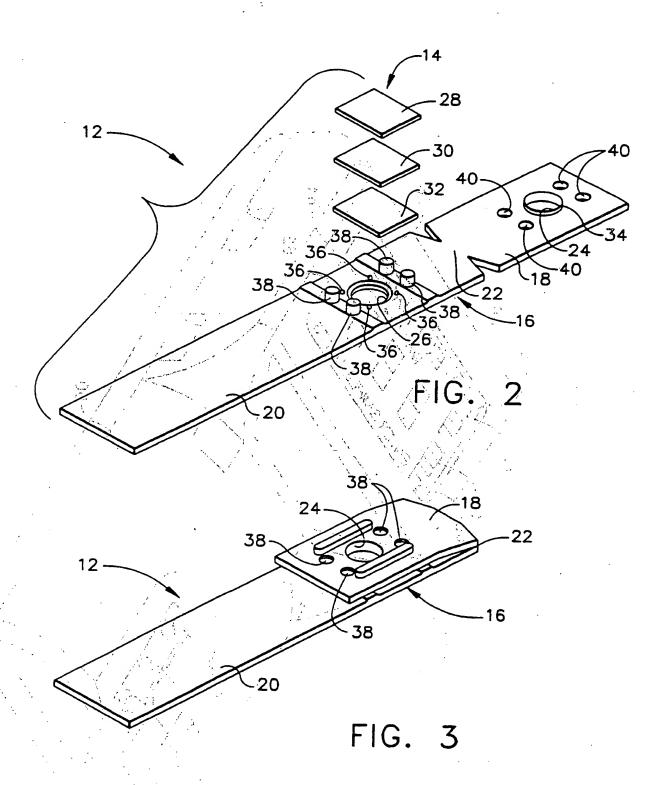
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use in analyzing a sample, each said test strip having an
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                                                                                                                                           adhesiveless carrier layer attached without compression to said
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                                                                                                                                         test strip;
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                                                                                                                                                                                                                               selecting a test strip of a predetermined color for a
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                                                                                                                                                                                                                           depositing a test sample on the carrier layer of the
                                                                                                                                 selected test strip;
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                                                                            inserting said test strip into said measurement
                                                                                                                                 system;
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                                                                                                              operating said measurement system to conduct the
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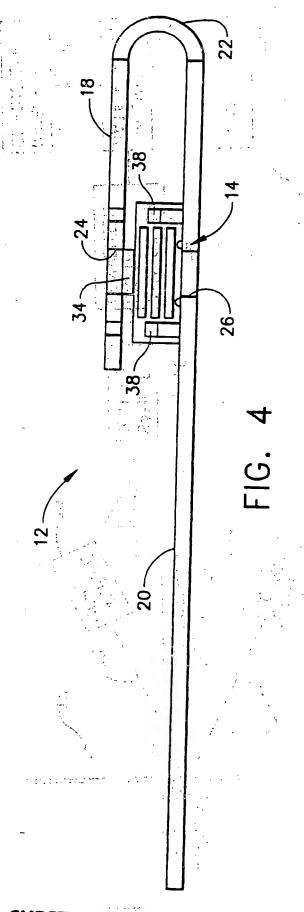
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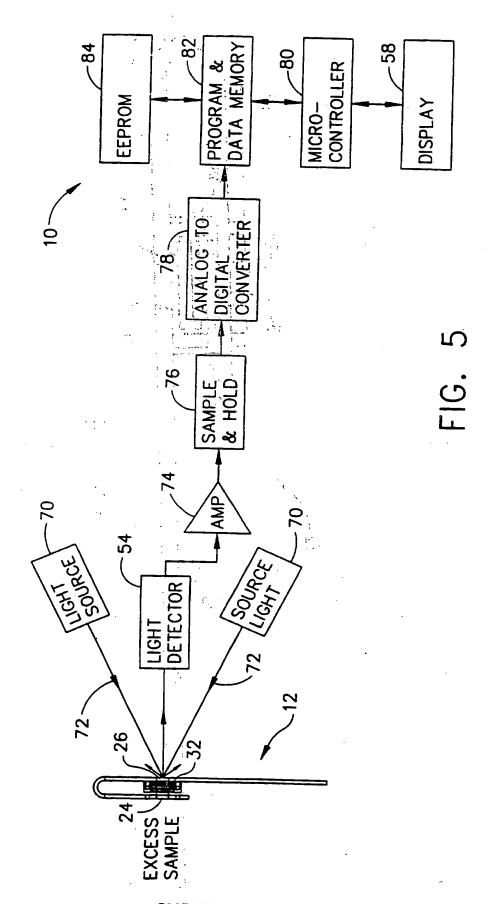


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ANY REFERENCE TO
FIGURE 6 SHALL BE
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(See Article 14(2))

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A. CLASSIFICATION OF SUBJECT MATTER IPC 6 G01N33/52 G01N21/84 G02F1/133

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 6 GO1N GO2F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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* Special categories of cited documents:	
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